

## Is it possible that antidepressants protect against COVID-19?

Anti-depresants and covid

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### Abstract

**Aim:** The neuroinflammatory hypothesis suggests that proinflammatory cytokines or the immune system may play a role in the etiopathogenesis of depression. COVID-19 affects older people the most because their immune systems are weakened. In this study, we aimed to examine the effect of using antidepressant use on mortality in patients infected with COVID-19.

**Material and Methods:** Our study was developed as a retrospective examination of unique central patient records. In our study, the diagnosis of COVID-19 diagnostics (U07.3) was between the ICD-10 classification (U07.3) and the diagnosis of depressive emotional state disorders (F31, F32, F33, F34) and patients with the diagnosis of COVID 19 confirmed by the test result were included.

**Results:** Considering the relationship between the use of antidepressants and mortality in COVID-19 patients, it was seen that the mortality rate was significantly lower in those using antidepressants ( $p < 0.05$ ). The presence of chronic disease was found to be significantly associated with mortality in COVID-19. The mortality rates of patients with chronic diseases were found to be higher ( $p < 0.01$ ).

**Discussion:** In our study, we found that antidepressants did not have any superiority over each other in terms of mortality in COVID-19 patients. However, when all anti depressants were evaluated in our study, we observed that drug use had a positive effect on statistically significant mortality ( $p < 0.05$ ). More enlightening results will emerge in larger case series.

### Keywords

Antidepressant; COVID-19; Pneumonia; Mortality

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## Introduction

Research in the field of psychoneuroimmunology shows that there is a mutual relationship between the immune system and the central nervous system. [1] The immune system has congenital and adaptive parts. Both sections have cellular and humoral components from which different cytokines are excreted. The cytokines produced by the non-specific immune system include interleukin (IL) -1, IL-6, tumor cornea factor (TNF) -A, Interferon (IFN) -A. The cytokines generated by the specific immune system are IL-2, IFN- $\gamma$ , IL-4, IL-10. They can be classified as "cytokines". Proinflammatory cytokines are IL-1, IL-2, IL-6, TNF- $\alpha$ , Inf-gamma; Anti-inflammatory cytokines (inhibitors of cytokine synthesis) are IL-4, IL-10, IL-12, IL-13, since cytokines like IL-13 have pro-inflammatory and anti-inflammatory functions [2,3].

Proinflammatory cytokines can be presented in response to exciting development, tissue damage, or psychosocial factors and transmitted between the immune system and the brain [4]. The rise in pro-inflammatory cytokines is generally adaptive, transient, and regulated by anti-inflammatory mechanisms. The neuroinflammatory hypothesis suggests that proinflammatory cytokines or the immune system may play a role in the etiopathogenesis of depression [3,5].

COVID-19 has caused the Chinese pandemic process in Wuhan, and around the world, and it affects older people the most because their immune systems are weakened. It is not known exactly if it was symptomatic in humans [6]. COVID-19 pneumonia is a disease that can be spread rapidly in the lungs and cause acute breathing syndrome (ARDS). The main cause of morbidity and mortality in patients with COVID-19 in the hospital is acute viral pneumonia that causes ARDS [7-9]. The average mortality in patients with COVID-19 with ARDS in all countries is 39% (World Health Organization. Clinical management of severe acute respiratory infection when novel coronavirus (nCoV) infection is suspected: Interim guidance. January 28, 2020.).

In this study, we aimed to examine the effect of antidepressant use on mortality in patients embedded by COVID-19.

## Material and Methods

### Ethical approval

The experimental methods and analyses used in this study were examined by the Institutional Review Board of Izmir Katip Çelebi University Non-interventional Clinical Studies, where the study was conducted considered appropriate to be performed (21.01.2021/0007).

### Study Design and Population

Our study was developed as a retrospective examination of unique central patient records. It takes place in Izmir Katip Çelebi University Ataturk Emergency Medical Clinic, with a single center in Izmir city center, with an annual number of patient applications. The emergency department of approximately 200,000. The duration of our research was between 01.10.2020-01.01.2021.

### Data Collection and Processing

#### Inclusion criteria

In our study, the diagnosis of COVID-19 diagnostics (U07.3) was between the ICD-10 classification (U07.3) and the diagnosis of

depressive emotional state disorders (F31, F32, F33, F34) and patients with the diagnosis of COVID-19 confirmed by the test results were included.

The active ingredients of the drugs used by our patients included in our study are "Duloxetine, escitalopram, fluoxetine, fluvoxamine, mirtazapine, paroxetine, sertraline, venlafaxine. There are tricyclic antidepressants, double-action antidepressants and serotonin reuptake inhibitors, and there is no limit to the types of these medications.

#### Exclusion criteria

Patients under the age of 18, COVID-19 diagnosis code (U07.3), entered in the COVID-19 diagnosis code (U07.3) as diagnosis/pre-diagnosis code (U07.3), with missing data were excluded from the study. The patient's medical records are verified through the hospital data processing database. The patient's demographic data, such as age, sex, vital signs, medical history and the results of the patient's physical examination, chronic medical history, medications used in the laboratory and image tests, and the rate of mortality rate from the disease were analyzed statistically.

#### Statistical Analysis

The data obtained were analyzed using the SPSS software for Windows version 21.0 (SPSS Inc., Chicago, USA. UU). Frequency distributions for categorical variables, means and standard deviation values were given as descriptive measures for numerical variables. Pearson's Chi-Square test was used as a categorical variable when comparing two independent groups. Any p-value of less than 0.05 was considered statistically significant.

## Results

A total of 1051 patients were included in the study. The mean age of the patients was  $47.65 \pm 17.46$  years. Four hundred ninety (46.6%) of the patients were female and 561 (53.4%) were male. There was no significant difference between gender and mortality ( $p = 0.931$ ). The mean age of the deceased patients was  $68.23 \pm 15.69$  years and the average age of the survivors was  $45.34 \pm 16.08$  years. Considering the relationship between the use of antidepressants and mortality in COVID-19 patients, it was seen that the mortality rate was significantly lower in those using antidepressants ( $p < 0.05$ ) (Table 1).

**Table 1.** The Relationship Between Antidepressant Use and Mortality

		Antidepressant use		
		No	Yes	Total
Mortality	No	842	103	945
	Yes	101	5	106
Total	943	108	1051	

Pearson's Chi-square test was used

**Table 2.** Relationship between the Presence of Chronic Disease and Mortality

		Chronic Disease Presence		
		No	Yes	Total
Mortality	No	683	262	945
	Yes	41	65	106
Total	724	327	1051	

The presence of chronic disease was found to be significantly associated with mortality in COVID-19. The mortality rates of patients with chronic diseases were found to be higher ( $p < 0.01$ ) (Table 2). When the mortality rates were compared according to the antidepressant drugs used by the patients, it was observed that there was no significant difference ( $p = 0.65$ ) (Table 1).

## Discussion

It is generally accepted that psychiatric diseases such as depression, schizophrenia, panic, and bipolar disorder derive directly from the dysfunction of the nerve cells, the working system disorder. In recent years, another hypothesis, called the "neuroinflammation hypothesis" has emerged. According to this hypothesis, these diseases occur due to the negative effect of the immune system cells on nervous system cells and inflammatory events in neurons. In summary, we can say that antidepressants directly and indirectly strengthen the immune system, and people who use these drugs have a somewhat more protective shield than other people [13].

As it is known, stress mainly affects the functions of the Hypothalamus-pituitary-adrenal axis (HPA) axis. Under stress, corticotropin-releasing hormone (CRH) is released from the hypothalamus, adrenocorticotropic hormone (ACTH) release is stimulated by the pituitary, and glucocorticoids release from the adrenal cortex increases [1,10]. The functioning of this system is regulated by the negative feedback mechanism. Cytokines cause desensitization of glucocorticoid receptors and prevent the functioning of negative feedback mechanism in the HPA axis. This results in a strong stimulation of HPA axis activity. Acute stress response occurs with activation of the HPA axis, but long-term problems arise when stress becomes chronic [10-12].

Antidepressants normalize by reducing pre-treatment high serum proinflammatory cytokine levels (IL-1 $\beta$ , IL-2, IL-6, TNF- $\alpha$  and INF- $\gamma$ ) [13]. In a meta-analysis evaluating publications investigating the effects of antidepressants on TNF- $\alpha$ , IL-6 and IL-1 $\beta$ , it was determined that depressive symptoms decreased after treatment, TNF- $\alpha$  levels did not change, but IL-1 $\beta$  and IL-6 levels decreased, and oxidative stress decrease [17].

It has been determined that SSRIs reduce IL-6 and TNF- $\alpha$  levels, but other antidepressants do not cause a decrease in cytokine levels. It was emphasized that while depression is improving, cytokine levels normalize, cytokines contribute to the development of depressive symptoms, and antidepressants reduce cytokine levels, which may contribute to the recovery from depression. [14] The results of our study support this hypothesis. Cytokine reduction and suppression of ILs and TNF alpha cause a decrease in inflammatory response. Accordingly, we think that the progression of ARDS in patients using antidepressants may be slower than in patients who do not use antidepressants.

Although it is not known exactly how the immunomodulatory effects of antidepressants emerge, the possible mechanisms are as follows: hypotheses such as regulation of central glucocorticoid receptor expression, reestablishment of glucocorticoid-mediated feedback mechanism, that is, improvement of glucocorticoid receptor sensitivity, adaptive modification of central monoaminergic neurotransmission,

down-regulation of the receptors on which cytokines and reduction of NO and PDE2 synthesis mediating central effects of cytokines [13,15,16]. Based on these hypotheses, we evaluated 8 different antidepressant drugs (duloxetine, escitalopram, fluoxetine, fluvoxamine, mirtazapine, paroxetine, sertraline and venlafaxine). Based on the antioxidant effect of reboxetine, in a study published in the literature, a significant relationship with mortality was found. However, in our study, we found that antidepressant drugs did not have any superiority over each other in terms of mortality in patients with COVID-19.

However, when all antidepressants were evaluated in our study, we observed that drug use had a statistically significant positive effect on mortality ( $p < 0.05$ ). More enlightening results will emerge in larger case series.

## Conclusion

It is considered that using antidepressants protects against COVID-19 Pneumonia and decreases mortality by diminishing stress hormones and probably supports immunity in a good way.

### Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

### Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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### Conflict of interest

None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

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